REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.114, are respectfully requested.

Status

Claims 1-20 are pending, and all stand rejected. *See Office Action mailed September 22, 2004, pp. 2-3.*[1] Applicants' Amendment and Reply of May 5, 2004, eliminated the 35 U.S.C. § 112, First Paragraph indefiniteness rejections and the minor claim informalities.

Summary of Amendments

Applicants amend the specification at page 5, lines 31-34 to correct a translation error. In the original application, the French expression "suspension aqueuse" was erroneously translated as "aqueous solution." The correct translation of "suspension aqueuse" is "aqueous suspension" as now appears in the amended paragraph.

Applicants amend Claim 1 to specify that "said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of the composition." The Specification supports the amendment at, e.g., p. 4, Lines 30-33. No new matter has been added.

Applicants cancel Claim 8 without prejudice or disclaimer.

[1] The Final Office Action Summary incorrectly states that Claims 14-20 are pending.

Applicants amend Claim 11 to read "wherein said composition is in the form of powder or granules, optionally contained in gelatin capsules." The Specification supports the amendment, e.g., original Claim 11. No new matter has been added.

Applicants add new Claims 21-46. The Specification supports those claims at, e.g., p. 3, Line 18 - p. 4, Line 24, and p. 5, lines 31-34. Specifically, Applicants have added claims reciting the ratio of fenofibrate/cellulose derivative (21); and claiming the suspension resulting from claim 11 (38). No new matter has been added.

Rejection Under 35 U.S.C. § 103(a) – Stamm and/or DeBoeck

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over U.S. Patent No. 6,074,670 to Stamm *et al.* ("Stamm") or U.S. Patent No. 5,545,628 to Deboeck *et al.* ("Deboeck") in view of Stamm. *Office Action, September 22, 2004, pp. 2-6.* Applicants traverse the rejection.

Neither of the cited references suggests the present invention, nor does the combination. Neither reference teaches or suggests the fabrication of a pharmaceutical composition comprising micronized fenofibrate present in an amount greater than 60% by weight of the composition, and a binding cellulose derivative of 2 to 15% by weight of the composition.

Stamm

Stamm teaches away from the present invention. Stamm states that a pharmaceutical composition of micronized fenofibrate can be formulated into a tablet wherein 20 to 50% by weight of the composition is fenofibrate (Stamm, col. 5, lines 1-7); and wherein the hydropyhilic polymer solubilizing agent is at least 20% by

weight of the composition (Stamm, col. 3, lines 11-23, "said hydrophilic polymer making up at least 20% by weight of (a)...." emphasis added).

The Examiner has taken the position that the claimed invention is mere optimization of the composition taught by Stamm. Applicants disagree. The claimed invention is outside the ranges taught by Stamm, and runs contrary to the teaching of Stamm. Thus, the claimed invention is not obvious over Stamm, or Stamm with DeBoeck.

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." MPEP §2144.05.II.A, *Optimization Within Prior Art Conditions Or Through Routine Experimentation* (emphasis added). Here, however, the cited art does not encompass the claimed invention, nor do the ranges of the art abut the claimed ranges. Rather, both the claimed ranges are substantially outside those of the reference.

Stamm unequivocally states that the hydrophilic polymer must be at least 20% by weight. (Stamm, col. 3, lines 11-23). Thus, the reference teaches that the hydrophilic polymer can not be below 20% by weight.

The reference also states that the fenofibrate represents up to 50% by weight of the composition. The reference does not explicitly state that the composition can not contain greater than 50% by weight fenofibrate, but neither does it suggest that compositions can be formulated having greater than 50% fenofibrate.

Stamm neither encompasses nor abuts the claimed invention, and thus the claimed invention is not merely optimization within prior art conditions or through routine experimentation.

Furthermore, the deviation from the cited reference is not optimization of a result-effective variable because the modification runs contrary to the desired result. "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP §2144.05.II.B. While it might be argued that applicants modified a result-effective variable, it was modified in a way that would have been expected to produce an effect opposite that intended, i.e., diminished dissolution. The result is unexpected, and thus nonobvious.

Fenofibrate is insoluble in water, and thus has poor dissolution and bioavailability on oral administration. Stamm purportedly overcomes that deficiency by, among other things, formulating a composition of micronized fenofibrate in a hydrosoluble carrier. The hydrosoluble carrier includes a hydrophilic polymer, which enhances dissolution of the fenofribrate. To achieve the desired dissolution profile, Stamm states that the hydrophilic polymer must be at least 20% of the composition, suggesting that greater quantities would produce a better dissolution profile.

In contrast, applicants modified the variable in the opposite direction, decreasing the hydrophilic polymer while improving the dissolution profile. Going contrary to the art is the antithesis of obviousness.

Stamm emphasizes that the fenofibrate composition includes, as a significant essential component, the hydrophilic polymer and that improved dissolution of the composition is allowed provided that the hydrophilic polymer represents at least 20% by weight of element (a); and preferably 25-45% by weight, or more than 25% by weight of element (a). Stamm, col. 5, lines 4-12. Stamm further states "the weight

ratio fenofibrate/hydrophilic polymer can, for example, be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1." According to Stamm's teaching, the fenofibrate represent from 5 to 50% by weight, preferably, from 20-45% by weight of element (a). Col. 4, line 66 - col. 5, line 7.

Further, the ratio fenofibrate/binding cellulose derivative of the claimed composition is between 5/1 and 15/1; while the ratio fenofibrate/hydrophilic polymer of Stamm is between 1/10 and 4/1.

Applicants' invention provides a fenofibrate composition having greater dissolution and bioavailability in a composition comprising greater than or equal to 60% micronized fenofibrate, a surfactant , and a binding cellulose derivative. The composition overcomes deficiencies of Stamm's compositions by using less binder and producing a formulation of equivalent dosage but smaller size. *See, e.g., Specification p. 3, lines 9-16; and p. 3, line 37 – p. 4, line 4.*

Prior to Applicants' invention, one would not have expected such properties, especially in light of Stamm's teaching that fenofibrate must be 50% (wt) or less, and the hydrophilic polymer must be at least 20% (wt). Applicants went squarely against Stamm by increasing fenofibrate above 50% (wt), and decreasing hydrophilic polymer below 20%. This is the antithesis of obviousness. Applicants respectfully request reconsideration and withdrawal of the rejection.

Deboeck

There is no suggestion or motivation to both combine and modify the teachings of Stamm and Deboeck to arrive at the present invention.

There are important differences between DeBoeck and Stamm. First, Deboeck permits a range of fenofibrate from 5 to 95%, but prefers a range from 45 to 55%. *Deboeck, col. 3, lines 49-62.*

Second, unlike both Applicants' and Stamm's compositions, Deboeck's compositions do not contain *micronized* fenofibrate.

Third, Deboeck teaches use of a molten solution of *non-micronized fenofibrate-polyglycolized glycerides*, which is subsequently cooled. Deboeck adds a cellulose derivative into the molten suspension as a stabilizer, which allegedly avoids the formation of fenofibrate crystals during cooling. *Deboeck, col. 2, lines 43-54.* Stamm, however, teaches the use of micronized fenofibrate, and that it must be formulated in an aqueous or organic solvent.

In DeBoeck, HPMC is cited as a suspension stabilizer to the molten solution of fenofibrate-polyglycolized glycerides. DeBoeck states: "the suspension stabilizer avoids the formation of fenofibrate crystals during cooling of the filled hard gelatin capsules." DeBoeck, col. 2, lines 44-55. DeBoeck teach the use of HPMC only when the fenofibrate composition contains polyglycolized glycerides. If the fenofibrate composition does not contain polyglycolized glycerides, there is no need of a suspension stabilizer such as HPMC.

Given the contrasting natures of Stamm and Deboeck with respect to the various components, one would not have been motivated to combine those two references. Even if one were so motivated, there has been no showing that such a combination would have been as claimed, or that it would have produced a pharmaceutical composition having the intended properties.

The rejection asserts that the combination of references is proper as the claims are directed to a composition and not the process of preparing the composition. However, the selection of materials is highly relevant to the properties of the resulting composition, and goes directly to the issue of motivation to combine. Further, the two references describe compositions containing substantially different constituents in substantially different quantities, and there is no showing of any motivation for selecting the teaching of one over the other in those aspects where the two references diverge. Nor is there any showing that such a motivating teaching, if there is one, would produce the claimed invention. Without some motivation to combine the references, and to resolve the differences between the two in a manner that would produce the claimed invention, there is no *prima facie* showing of obviousness. Accordingly, the rejection is improper and should be withdrawn.

From the foregoing, Applicants assert that the rejection does not establish a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the § 103(a) rejection of Claims 1-13 over Stamm, either alone or in combination with Deboeck.

CONCLUSION

The foregoing amendments and remarks overcome all outstanding rejections. Applicants respectfully request formal notification of allowance of all pending claims. If, however, the Examiner has any questions relating to this Amendment and Reply, or the application in general, applicants encourage the Examiner to contact their attorney by telephone at (703) 838-6526 to expedite examination and disposition of the case.

Respectfully submitted,
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Date: March 18, 2005

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